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# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Application Number | 09/970,020 |
| Filing Date | 10/03/2001 |
| First Named Inventor | Liu et al. |
| Art Unit | 1615 |
| Examiner Name | R. Joynes |
| Total Number of Pages in This Submission: 53 | Attorney Docket Number: 107223.139 |

## ENCLOSURES *(Check all that apply)*

- [✔] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [✔] Appeal Communication to Group **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [✔] Other Enclosure(s) (please Identify below):
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Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | |
|---|---|
| Firm or Individual name | Emily R. Whelan, Reg. No. 50,391 |
| Signature | Emily R Whelan |
| Date | 12/16/2003 |

## CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. §1.10

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| Typed or printed name | Maureen DiVito | | |
| Signature | Maureen DiVito | Date | 12/16/2003 |

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# FEE TRANSMITTAL for FY 2004

*Effective 10/01/2003. Patent fees are subject to annual revision.*

☒ Applicant claims small entity status. See 37 CFR 1.27

**TOTAL AMOUNT OF PAYMENT** ($) 165.00

| *Complete if Known* | |
|---|---|
| Application Number | 09/970,020 |
| Filing Dat | 10/03/2001 |
| First Named Inventor | Liu et al. |
| Examiner Name | R. Joynes |
| Art Unit | 1615 |
| Attorney Docket No. | 107223.139 |

## METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 08-0219
Deposit Account Name: Hale and Dorr LLP

**The Director is authorized to:** *(check all that apply)*

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## FEE CALCULATION

### 1. BASIC FILING FEE

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 1001 | 770 | 2001 | 385 | Utility filing fee | |
| 1002 | 340 | 2002 | 170 | Design filing fee | |
| 1003 | 530 | 2003 | 265 | Plant filing fee | |
| 1004 | 770 | 2004 | 385 | Reissue filing fee | |
| 1005 | 160 | 2005 | 80 | Provisional filing fee | |

**SUBTOTAL (1)** ($) 0.00

### 2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

| | | Extra Claims | | Fee from below | | Fee Paid |
|---|---|---|---|---|---|---|
| Total Claims | | -20** = | | X | = | |
| Independent Claims | | - 3** = | | X | = | |
| Multiple Dependent | | | | 0 | = | 0 |

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description |
|---|---|---|---|---|
| 1202 | 18 | 2202 | 9 | Claims in excess of 20 |
| 1201 | 86 | 2201 | 43 | Independent claims in excess of 3 |
| 1203 | 290 | 2203 | 145 | Multiple dependent claim, if not paid |
| 1204 | 86 | 2204 | 43 | ** Reissue independent claims over original patent |
| 1205 | 18 | 2205 | 9 | ** Reissue claims in excess of 20 and over original patent |

**SUBTOTAL (2)** ($) 0.00

***or number previously paid, if greater; For Reissues, see above*

## FEE CALCULATION (continued)

### 3. ADDITIONAL FEES

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 1051 | 130 | 2051 | 65 | Surcharge - late filing fee or oath | |
| 1052 | 50 | 2052 | 25 | Surcharge - late provisional filing fee or cover sheet | |
| 1053 | 130 | 1053 | 130 | Non-English specification | |
| 1812 | 2,520 | 1812 | 2,520 | For filing a request for *ex parte* reexamination | |
| 1804 | 920* | 1804 | 920* | Requesting publication of SIR prior to Examiner action | |
| 1805 | 1,840* | 1805 | 1,840* | Requesting publication of SIR after Examiner action | |
| 1251 | 110 | 2251 | 55 | Extension for reply within first month | |
| 1252 | 420 | 2252 | 210 | Extension for reply within second month | |
| 1253 | 950 | 2253 | 475 | Extension for reply within third month | |
| 1254 | 1,480 | 2254 | 740 | Extension for reply within fourth month | |
| 1255 | 2,010 | 2255 | 1,005 | Extension for reply within fifth month | |
| 1401 | 330 | 2401 | 165 | Notice of Appeal | |
| 1402 | 330 | 2402 | 165 | Filing a brief in support of an appeal | 165.00 |
| 1403 | 290 | 2403 | 145 | Request for oral hearing | |
| 1451 | 1,510 | 1451 | 1,510 | Petition to institute a public use proceeding | |
| 1452 | 110 | 2452 | 55 | Petition to revive - unavoidable | |
| 1453 | 1,330 | 2453 | 665 | Petition to revive - unintentional | |
| 1501 | 1,330 | 2501 | 665 | Utility issue fee (or reissue) | |
| 1502 | 480 | 2502 | 240 | Design issue fee | |
| 1503 | 640 | 2503 | 320 | Plant issue fee | |
| 1460 | 130 | 1460 | 130 | Petitions to the Commissioner | |
| 1807 | 50 | 1807 | 50 | Processing fee under 37 CFR 1.17(q) | |
| 1806 | 180 | 1806 | 180 | Submission of Information Disclosure Stmt | |
| 8021 | 40 | 8021 | 40 | Recording each patent assignment per property (times number of properties) | |
| 1809 | 770 | 2809 | 385 | Filing a submission after final rejection (37 CFR 1.129(a)) | |
| 1810 | 770 | 2810 | 385 | For each additional invention to be examined (37 CFR 1.129(b)) | |
| 1801 | 770 | 2801 | 385 | Request for Continued Examination (RCE) | |
| 1802 | 900 | 1802 | 900 | Request for expedited examination of a design application | |

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 165.00

## SUBMITTED BY

(Complete *(if applicable)*)

| Name (Print/Type) | Emily R. Whelan | Registration No. (Attorney/Agent) | 50,391 | Telephone | 617-526-6567 |
|---|---|---|---|---|---|
| Signature | Emily R Whelan | | | Date | 12/16/2003 |

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PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant: | Liu et al. | Examiner: | R. Joynes |
| Serial No.: | 09/970,020 | Art Unit: | 1615 |
| Filed: | October 3, 2001 | Confirmation No.: | 8697 |
| Entitled: | **Developing A Delivery System For Multi-Pharmaceutical Active Materials at Various Release Rates** | Atty. Docket No.: | 107223-139 US |

**CERTIFICATION UNDER 37 C.F.R. § 1.10**

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December 16, 2003
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Maureen DiVito
Maureen DiVito

## APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Mail Stop Appeal Brief – Patents
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Sir:

This is an Appeal Brief pursuant to the Notice of Appeal filed on October 23, 2003, appealing the rejection of claims 24-54 in the Final Office Action of July 24, 2003. This Brief is being filed in triplicate.

## I. REAL PARTY IN INTEREST

The real party in interest is Penwest Pharmaceuticals Co., the assignee of the present application.

## II. RELATED APPEALS AND INTERFERENCES

The Appellants, the Appellants' legal representatives, and the Assignee are not aware of any pending appeal or interference that would directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

## III. STATUS OF THE CLAIMS

Claims 24-54 are pending in the application, and are finally rejected. Claims 1-23 were canceled during prosecution. Claims 24-54 are appealed.

## IV. STATUS OF AMENDMENTS

The claims were last amended in the Response and Amendment under 37 C.F.R. § 1.111 dated May 8, 2003. No amendment has been submitted subsequent to final rejection in the Final Office Action of July 24, 2003. A copy of the pending claims is attached in the Appendix to this Appeal Brief.

## V. SUMMARY OF THE INVENTION

The invention provides a novel controlled release delivery system for administering more than one pharmaceutically effective agent. The delivery system is particularly useful for administering the enantiomers of chiral drugs, for example, the (+) and (-) enantiomers of tramadol. *See* Specification at page 3, line 27 – page 4, line 12.

The invention includes pharmaceutical compositions that provide an immediate release formulation of one enantiomer of a chiral compound, and a controlled release formulation of another enantiomer of a chiral compound. *See* Specification at page 16, lines 13-16. Controlled release is effected by a heteropolysaccharide and polysaccharide gum excipient known as TIMERx®. *See* Specification at page 15, lines 7-10 and Example 1, page 30, line 2 – page 35, line 5; *see also* "TIMERx" in U.S. Patent and Trademark Office, Trademark Database at www.uspto.gov. The application discloses particularly useful TIMERx® formulations containing xanthan gum and locust bean gum. *See* Specification at Example 1, page 30, line 2 – page 35, line 5. The claimed compositions are formulated for oral administration, for example, as a bi-layered tablet. *See* Specification at page 17, lines 22-29 and page 19, lines 15-16.

The pharmaceutical compositions of the invention are particularly advantageous for administering chiral drugs whose enantiomers are both pharmaceutically effective, but differ from one another, *e.g.*, in potency, pharmacokinetics, and/or safety profile. The claimed compositions allow for administration of both enantiomers at once, but with different delivery rates, thus enhancing the overall safety and efficacy of the chiral drug. *See* Specification at page 1, line 28 – page 3, line 6 and page 16, lines 13-16. Varying the amount and make-up of the

TIMERx® in a particular composition allows for manipulation of the drug release profile as desired. *See* Specification at Example 1, page 30, line 2 – page 35, line 5.

## VI. ISSUE

Are claims 24-54 unobvious under 35 U.S.C. §103(a) over Gilbert et al., WO 98/40053 in combination with Baichwal et al., U.S. Patent No. 4,994,276?

## VII. GROUPING OF CLAIMS

Claims 24-54 stand or fall together.

## VIII. ARGUMENT

Claims 24-54 are unobvious under 35 U.S.C. §103(a) over Gilbert et al., WO 98/40053 ("Gilbert") in combination with Baichwal et al., U.S. Patent No. 4,994,276 ("Baichwal").

Gilbert teaches a dosage form having separate portions (*e.g.*, a bi-layer tablet), each portion containing one enantiomer of a chiral drug (*e.g.*, tramadol or warfarin). The enantiomers are released from the dosage form at different rates. Gilbert refers generally to employing conventional controlled release technology, but does not disclose or suggest a heteropolysaccharide and polysaccharide gum excipient. *See* Abstract and page 6, lines 30-35.

Baichwal teaches a heteropolysaccharide and polysaccharide gum excipient for controlled release delivery of a drug. *See* column 4, lines 8-54. However, Baichwal does not teach or suggest use of the disclosed excipient in a pharmaceutical composition containing both immediate release and controlled release formulations, or a pharmaceutical composition providing separate delivery rates for enantiomers of a chiral drug.

A *prima facie* case of obviousness over the combination of Gilbert and Baichwal has not been established. *Prima facie* obviousness requires some teaching, suggestion, or motivation to combine the references. The motivation to combine may come from the nature of the problem, but more often is found in the teachings of the cited references, or the knowledge of one of ordinary skill in the art that certain references are particularly important. The motivation to combine must not be based on improper hindsight in view of the claimed invention. *See In re Rouffet*, 149 F.3d 1350, 1355, 1358 (Fed. Cir. 1998). The showing of motivation to combine must be clear and particular, based on actual evidence, and not merely broad conclusory

statements regarding the teachings of multiple references. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (citation omitted).

> To prevent the use of hindsight based on the invention to defeat patentability ... the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed. ... [The examiner should] explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. *In re Rouffet*, 49 F.3d at 1357-58.

Prior to Appellants' invention, there would have been no motivation for one of ordinary skill in the art to combine the teachings of Gilbert and Baichwal. Nothing in Baichwal suggests use of the disclosed sustained release excipient in two-part formulations providing separate delivery rates for enantiomers of a chiral drug. Similarly, nothing in Gilbert suggests use of the particular excipient of Baichwal in the disclosed two-part enantiomer formulations. The Examiner admitted that Gilbert does not teach a heteropolysaccharide and polysaccharide gum excipient, but asserted that Gilbert teaches the use of any conventional controlled release system to achieve the desired formulation, and that Baichwal provides one such conventional controlled release system. The Examiner argued further that one would be motivated to use the excipient of Baichwal in the formulations of Gilbert because Baichwal teaches that the disclosed excipient can be used with a wide variety of drugs and is easily compressible and inexpensive. *See* Final Office Action of July 24, 2003 at page 3, lines 4-7 and 16-22; page 4, lines 12-18; and page 5, lines 8-16.

The Examiner's conclusory statements do not provide sufficient evidence of motivation to combine to support a *prima facie* case of obviousness. In particular, the Examiner has not pointed out any specific reason why one of ordinary skill in the art, without the benefit of Appellants' disclosure, would select Baichwal's excipient from the thousands of known controlled release delivery systems for use in the two-part enantiomer formulations of Gilbert. Conclusory statements regarding the general advantages of Baichwal's excipient (*e.g.*, noting that it is inexpensive and can be used with a variety of drugs) do not suffice in view of the vast

number of available controlled release technologies, each of which may have their own particular advantages.

Appellants' response dated May 8, 2003 described a review of the PTO patent database at www.uspto.gov for patents issued from 1976 to May 6, 2003. Boolean searches of the database revealed **22,097** hits for the terms "controlled," "release," and "pharmaceutical"; **17,479** hits for the terms "sustained," "release," and "pharmaceutical"; and **11,214** hits for the terms "extended," and "release," and "pharmaceutical." In view of these search results, Appellants respectfully requested an explanation why one skilled in the art would be motivated to select Baichwal from among the more than 22,000 patents from 1976 to the present in the PTO database that describe conventional controlled-release technology. *See* Response and Amendment of May 8, 2003 at page 9, line 29 – page 10, line 8. In the Final Office Action of July 24, 2003, the Examiner failed to provide the requested explanation, instead simply dismissing Appellants' search results as "very broad and unpersuasive." To support this position, the Examiner stated that Appellants provided no evidence that all of the 22,097 references found by the search teach a controlled release system, and rather showed only that the three words appeared in the same reference. *See* Final Office Action at page 5, lines 17-22.

To address the Examiner's concern about the relevance of the identified references, Appellants performed an additional search of the PTO patent database on December 5, 2003, using the following search query: ("controlled release formulation" or "sustained release formulation" or "extended release formulation") and "pharmaceutical." Even this much more limited search, which mandates that the identified references disclose a controlled release formulation, revealed **2,061** hits. It should be remembered that these search results represent only U.S. patents issued since 1976, and the broader patent and scientific literature would certainly provide many more relevant search results. In view of these additional search results, Appellants again respectfully submit that a clear explanation should be provided why one of ordinary skill in the art would select the Baichwal reference from among the thousands of available references disclosing conventional controlled release technology. Without such an explanation, Appellants maintain that there simply would have been no motivation for one of ordinary skill in the art to select the sustained release excipient of Baichwal for use in the formulation described by Gilbert.

Gilbert itself expands on a large number of potential dosage forms, including oral, rectal, transdermal, ophthalmic, pulmonary, and injectable formulations of various types, *e.g.*, multi-particulates, multiple tablets, osmotic pumps, bi-layered tablets, transdermal patches, polymer implants, and aerosols. *See* page 5, line 31 – page 8, line 8. As discussed above, in describing these dosage forms, Gilbert refers to adjusting the rate of release of the enantiomers using "any conventional controlled-release mechanism, for instance, matrix (ie. erosion diffusion), coating, or osmotic." *See, e.g.,* page 6, lines 9-14. In the Examples, Gilbert teaches controlled-release tablets and bi-layer tablets prepared with a particular controlled release excipient, namely, hydroxypropyl methyl cellulose (HPMC). *See* Examples 2-3, page 9, line 15 – page 10, line 17. The Examiner has not provided any reason why one of ordinary skill in the art would choose to prepare the formulations of Gilbert using any particular undisclosed conventional controlled release technology, rather than simply using HPMC, which Gilbert specifically teaches and exemplifies.

In sum, given the extremely large number of "conventional controlled release mechanisms," and Gilbert's exemplification of HPMC in particular, there would be no motivation to select the particular excipient of Baichwal for use in Gilbert's two-part formulations. In the absence of any motivation to combine the cited references, Appellants' claims are not obvious over Gilbert in view of Baichwal. *See In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (claimed compound not obvious where cited reference teaches vast number of compounds and discloses typical or preferred compounds different from claimed compound, and thus does not suggest selection of claimed compound) (citing *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) (claimed nucleic acid sequences not obvious over reference teaching almost infinite possibilities and not suggesting why one would choose the claimed sequences)); *In re Herschler*, 591 F.2d 693, 702 (C.C.P.A. 1979) (claimed combination of steroid and solvent DMSO not obvious where references teach general utility of DMSO as a solvent but there is no suggestion to choose DMSO from among countless numbers of solvents).

The U.S. Court of Appeals for the Federal Circuit has warned that it is improper to "use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Furthermore, "the best defense against hindsight-based obviousness analysis is rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art

references." *Ecolochem, Inc. v. Southern California Edison Co.*, 277 F.3d 1361, 1371 (Fed. Cir. 2000) (citation omitted). With respect to Appellants' claimed invention, there has been no showing of any motivation to combine the cited references, so *prima facie* obviousness has not been established, and the obviousness rejection is improper.

Accordingly, Appellants request that the Board of Patent Appeals and Interferences reverse the rejection under 35 U.S.C. § 103, and remand this case to the Examiner to withdraw the rejection and enter a Notice of Allowance.

## IX. CONCLUSION

For the reasons advanced above, Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejection, remand the application to the Examiner, and direct the Examiner to issue a Notice of Allowance.

Please deduct the $165.00 fee for filing an appeal brief from our Deposit Account No. 08-0219. No other fees are believed to be due. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

Respectfully Submitted,

Emily R Whelan

Emily R. Whelan
Registration No. 50,391

Dated: 12/16/03

Hale and Dorr, LLP
60 State Street
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617-526-5000 (facsimile)

## APPENDIX: Pending Claims

24. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of an immediate release formulation comprising a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof; and a controlled release formulation comprising a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a heteropolysaccharide and polysaccharide gum excipient.

25. The composition of claim 24, wherein the ratio of the heteropolysaccharide and polysaccharide gum excipient to (+) chiral compound enantiomer or pharmaceutically acceptable salt thereof is between about 1:3 to 3:1.

26. The composition of claim 24, wherein the heteropolysaccharide and polysaccharide gum excipient comprises locust bean gum and xanthan gum.

27. The composition of claim 24, wherein the controlled release formulation comprises a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose.

28. The composition of claim 24, wherein the controlled release formulation comprises a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 15% locust bean gum, 15% xanthan gum, 60% dextrose, and 10% calcium sulfate.

29. The composition of claim 24, wherein the composition is a bi-layered tablet.

30. The composition of claim 24, wherein the compound of the (+) and (-) chiral compound enantiomers is selected from the group consisting of warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine, aminoglutethimide, alfuzosin, celiprolol, cisapride, disopyramide, fenoldopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thioctic acid, thiopental, and zacopride.

31. The composition of claim 24, wherein, when measured by the USP type II dissolution method, the *in vitro* dissolution rate for the controlled release (CR) formulation and the immediate release (IR) formulation are:

| Time (hours) | % CR Release | % IR Release |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-60 % | 20-100 % |
| 0.5 | 0-65 % | 20-100 % |
| 1.0 | 5-70 % | 25-100 % |
| 2.0 | 5-75 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 10-100 % | 30-100 % |
| 8.0 | 20-100 % | 40-100 % |
| 10.0 | 25-100 % | 45-100 % |
| 12.0 | 25-100 % | 45-100 % |
| 18.0 | 35-100 % | 50-100 % |
| 24.0 | 35-100 % | 50-100 %. |

32. The composition of claim 24, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at different mass quantities.

33. The composition of claim 24, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at a percent ratio selected from the following table:

| (+) enantiomer | (-) enantiomer |
|---|---|
| 2 | 1 |
| 3 | 1 |
| 4 | 1 |
| 5 | 1 |
| 10 | 1 |
| 1 | 2 |
| 1 | 3 |
| 1 | 4 |
| 1 | 5 |
| 1 | 10. |

34. The composition of claim 24, wherein about 90% of the (+) chiral compound enantiomer and about 90% of the (-) chiral compound enantiomer are released within about 12 hours of administration.

35. The composition of claim 24, wherein when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral compound enantiomer plasma concentrations:

| Time (hours) | (+) Enantiomer | (-) Enantiomer |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-60 % | 0-100 % |
| 0.5 | 0-65 % | 0-100 % |
| 1.0 | 5-70 % | 25-100 % |
| 2.0 | 5-75 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 20-100 % | 30-100 % |
| 8.0 | 20-100 % | 20-100 % |
| 10.0 | 20-100 % | 20-100 % |
| 12.0 | 10-100 % | 0-90 % |
| 18.0 | 0-80 % | 0-80 % |
| 24.0 | 0-80 % | 0-80 %. |

36. The composition of claim 24, wherein, when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral drug enantiomer plasma concentrations:

| Time (hours) | (+) Enantiomer | (-) Enantiomer |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-40 % | 0-100 % |
| 0.5 | 0-45 % | 0-100 % |
| 1.0 | 5-50 % | 25-100 % |
| 2.0 | 5-55 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |

| | | |
|---|---|---|
| 6.0 | 20-100 % | 30-100 % |
| 8.0 | 20-100 % | 20-100 % |
| 10.0 | 10-100 % | 20-100 % |
| 12.0 | 0-80 % | 10-90 % |
| 18.0 | 0-80 % | 0-80 % |
| 24.0 | 0-80 % | 0-80 %. |

37. The composition of claim 24, wherein the compound of the (+) and (-) chiral compound enantiomers is tramadol.

38. The composition of claim 37, wherein the (+) tramadol enantiomer and the (-) tramadol enantiomer are present in the composition at a percent ratio of 3:1.

39. The composition of claim 37, wherein the (+) tramadol enantiomer and the (-) tramadol enantiomer are present in the composition at a percent ratio of 2:1.

40. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of an immediate release formulation comprising a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof; and a controlled release formulation comprising a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a heteropolysaccharide and polysaccharide gum excipient.

41. The composition of claim 40, wherein the ratio of the heteropolysaccharide and polysaccharide gum excipient to (-) chiral compound enantiomer or pharmaceutically acceptable salt thereof is between about 1:3 to 3:1.

42. The composition of claim 40, wherein the heteropolysaccharide and polysaccharide gum excipient comprises locust bean gum and xanthan gum.

43. The composition of claim 40, wherein the controlled release formulation comprises a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose.

44. The composition of claim 40, wherein the controlled release formulation comprises a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 15% locust bean gum, 15% xanthan gum, 60% dextrose, and 10% calcium sulfate.

45. The composition of claim 40, wherein the composition is a bi-layered tablet.

46. The composition of claim 40, wherein the compound of the (+) and (-) chiral compound enantiomers is selected from the group consisting of warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine, aminoglutethimide, alfuzosin, celiprolol, cisapride, disopyramide, fenoldopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thioctic acid, thiopental, and zacopride.

47. The composition of claim 40, wherein, when measured by the USP type II dissolution method, the *in vitro* dissolution rate for the controlled release (CR) formulation and the immediate release (IR) formulation are:

| Time (hours) | % CR Release | % IR Release |
|---|---|---|
| 0 | 0% | 0% |

| | | |
|---|---|---|
| 0.3 | 0-60 % | 20-100 % |
| 0.5 | 0-65 % | 20-100 % |
| 1.0 | 5-70 % | 25-100 % |
| 2.0 | 5-75 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 10-100 % | 30-100 % |
| 8.0 | 20-100 % | 40-100 % |
| 10.0 | 25-100 % | 45-100 % |
| 12.0 | 25-100 % | 45-100 % |
| 18.0 | 35-100 % | 50-100 % |
| 24.0 | 35-100 % | 50-100 %. |

48. The composition of claim 40, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at different mass quantities.

49. The composition of claim 40, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at a percent ratio selected from the following table:

| (+) enantiomer | (-) enantiomer |
|---|---|
| 2 | 1 |
| 3 | 1 |
| 4 | 1 |
| 5 | 1 |
| 10 | 1 |

| | |
|---|---|
| 1 | 2 |
| 1 | 3 |
| 1 | 4 |
| 1 | 5 |
| 1 | 10. |

50. The composition of claim 40, wherein about 90% of the (+) chiral compound enantiomer and about 90% of the (-) chiral compound enantiomer are released within about 12 hours of administration.

51. The composition of claim 40, wherein when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral compound enantiomer plasma concentrations:

| Time (hours) | (+) Enantiomer | (-) Enantiomer |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-60 % | 0-100 % |
| 0.5 | 0-65 % | 0-100 % |
| 1.0 | 5-70 % | 25-100 % |
| 2.0 | 5-75 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 20-100 % | 30-100 % |
| 8.0 | 20-100 % | 20-100 % |
| 10.0 | 20-100 % | 20-100 % |
| 12.0 | 10-100 % | 0-90 % |

| | | |
|---|---|---|
| 18.0 | 0-80 % | 0-80 % |
| 24.0 | 0-80 % | 0-80 %. |

52. The composition of claim 40, wherein, when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral drug enantiomer plasma concentrations:

| Time (hours) | (+) Enantiomer | (-) Enantiomer |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-40 % | 0-100 % |
| 0.5 | 0-45 % | 0-100 % |
| 1.0 | 5-50 % | 25-100 % |
| 2.0 | 5-55 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 20-100 % | 30-100 % |
| 8.0 | 20-100 % | 20-100 % |
| 10.0 | 10-100 % | 20-100 % |
| 12.0 | 0-80 % | 10-90 % |
| 18.0 | 0-80 % | 0-80 % |
| 24.0 | 0-80 % | 0-80 %. |

53. The composition of claim 40, wherein the compound is tramadol.

54. A bi-layered, orally administrable tablet comprising:

(a) a controlled release formulation comprising about 5.4% by weight (+) tramadol or a pharmaceutically acceptable salt thereof; about 37.7% by weight of a controlled release

delivery system; about 16.2% by weight silicified microcrystalline cellulose; and about 0.6% by weight magnesium stearate; wherein the controlled release delivery system comprises 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose; and

(b) an immediate release formulation comprising about 16.2% by weight (-) tramadol or a pharmaceutically acceptable salt thereof; about 10.8% by weight silicified microcrystalline cellulose; about 10.8% lactose fast flow; about 2.2% sodium starch glycolate and about 0.3 % by weight magnesium stearate;

wherein the % by weight is based on the weight of the bi-layered, orally administrable tablet.

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant: | Liu et al. | Examiner: | R. Joynes |
| Serial No.: | 09/970,020 | Art Unit: | 1615 |
| Filed: | October 3, 2001 | Confirmation No.: | 8697 |
| Entitled: | **Developing A Delivery System For Multi-Pharmaceutical Active Materials at Various Release Rates** | Atty. Docket No.: | 107223-139 US |

**CERTIFICATION UNDER 37 C.F.R. § 1.10**

I hereby certify that the attached papers are being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" Mailing Label No. EV207558766US addressed to: **Mail Stop Appeal Brief - Patents**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

December 16, 2003
Date of Signature and of Mailing

Maureen DiVito
Maureen DiVito

## APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an Appeal Brief pursuant to the Notice of Appeal filed on October 23, 2003, appealing the rejection of claims 24-54 in the Final Office Action of July 24, 2003. This Brief is being filed in triplicate.

## I. REAL PARTY IN INTEREST

The real party in interest is Penwest Pharmaceuticals Co., the assignee of the present application.

## II. RELATED APPEALS AND INTERFERENCES

The Appellants, the Appellants' legal representatives, and the Assignee are not aware of any pending appeal or interference that would directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

## III. STATUS OF THE CLAIMS

Claims 24-54 are pending in the application, and are finally rejected. Claims 1-23 were canceled during prosecution. Claims 24-54 are appealed.

## IV. STATUS OF AMENDMENTS

The claims were last amended in the Response and Amendment under 37 C.F.R. § 1.111 dated May 8, 2003. No amendment has been submitted subsequent to final rejection in the Final Office Action of July 24, 2003. A copy of the pending claims is attached in the Appendix to this Appeal Brief.

## V. SUMMARY OF THE INVENTION

The invention provides a novel controlled release delivery system for administering more than one pharmaceutically effective agent. The delivery system is particularly useful for administering the enantiomers of chiral drugs, for example, the (+) and (-) enantiomers of tramadol. *See* Specification at page 3, line 27 – page 4, line 12.

The invention includes pharmaceutical compositions that provide an immediate release formulation of one enantiomer of a chiral compound, and a controlled release formulation of another enantiomer of a chiral compound. *See* Specification at page 16, lines 13-16. Controlled release is effected by a heteropolysaccharide and polysaccharide gum excipient known as TIMERx®. *See* Specification at page 15, lines 7-10 and Example 1, page 30, line 2 – page 35, line 5; *see also* "TIMERx" in U.S. Patent and Trademark Office, Trademark Database at www.uspto.gov. The application discloses particularly useful TIMERx® formulations containing xanthan gum and locust bean gum. *See* Specification at Example 1, page 30, line 2 – page 35, line 5. The claimed compositions are formulated for oral administration, for example, as a bi-layered tablet. *See* Specification at page 17, lines 22-29 and page 19, lines 15-16.

The pharmaceutical compositions of the invention are particularly advantageous for administering chiral drugs whose enantiomers are both pharmaceutically effective, but differ from one another, *e.g.*, in potency, pharmacokinetics, and/or safety profile. The claimed compositions allow for administration of both enantiomers at once, but with different delivery rates, thus enhancing the overall safety and efficacy of the chiral drug. *See* Specification at page 1, line 28 – page 3, line 6 and page 16, lines 13-16. Varying the amount and make-up of the

TIMERx® in a particular composition allows for manipulation of the drug release profile as desired. *See* Specification at Example 1, page 30, line 2 – page 35, line 5.

## VI. ISSUE

Are claims 24-54 unobvious under 35 U.S.C. §103(a) over Gilbert et al., WO 98/40053 in combination with Baichwal et al., U.S. Patent No. 4,994,276?

## VII. GROUPING OF CLAIMS

Claims 24-54 stand or fall together.

## VIII. ARGUMENT

Claims 24-54 are unobvious under 35 U.S.C. §103(a) over Gilbert et al., WO 98/40053 ("Gilbert") in combination with Baichwal et al., U.S. Patent No. 4,994,276 ("Baichwal").

Gilbert teaches a dosage form having separate portions (*e.g.*, a bi-layer tablet), each portion containing one enantiomer of a chiral drug (*e.g.*, tramadol or warfarin). The enantiomers are released from the dosage form at different rates. Gilbert refers generally to employing conventional controlled release technology, but does not disclose or suggest a heteropolysaccharide and polysaccharide gum excipient. *See* Abstract and page 6, lines 30-35.

Baichwal teaches a heteropolysaccharide and polysaccharide gum excipient for controlled release delivery of a drug. *See* column 4, lines 8-54. However, Baichwal does not teach or suggest use of the disclosed excipient in a pharmaceutical composition containing both immediate release and controlled release formulations, or a pharmaceutical composition providing separate delivery rates for enantiomers of a chiral drug.

A *prima facie* case of obviousness over the combination of Gilbert and Baichwal has not been established. *Prima facie* obviousness requires some teaching, suggestion, or motivation to combine the references. The motivation to combine may come from the nature of the problem, but more often is found in the teachings of the cited references, or the knowledge of one of ordinary skill in the art that certain references are particularly important. The motivation to combine must not be based on improper hindsight in view of the claimed invention. *See In re Rouffet*, 149 F.3d 1350, 1355, 1358 (Fed. Cir. 1998). The showing of motivation to combine must be clear and particular, based on actual evidence, and not merely broad conclusory

statements regarding the teachings of multiple references. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (citation omitted).

> To prevent the use of hindsight based on the invention to defeat patentability ... the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed. ... [The examiner should] explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. *In re Rouffet*, 49 F.3d at 1357-58.

Prior to Appellants' invention, there would have been no motivation for one of ordinary skill in the art to combine the teachings of Gilbert and Baichwal. Nothing in Baichwal suggests use of the disclosed sustained release excipient in two-part formulations providing separate delivery rates for enantiomers of a chiral drug. Similarly, nothing in Gilbert suggests use of the particular excipient of Baichwal in the disclosed two-part enantiomer formulations. The Examiner admitted that Gilbert does not teach a heteropolysaccharide and polysaccharide gum excipient, but asserted that Gilbert teaches the use of any conventional controlled release system to achieve the desired formulation, and that Baichwal provides one such conventional controlled release system. The Examiner argued further that one would be motivated to use the excipient of Baichwal in the formulations of Gilbert because Baichwal teaches that the disclosed excipient can be used with a wide variety of drugs and is easily compressible and inexpensive. *See* Final Office Action of July 24, 2003 at page 3, lines 4-7 and 16-22; page 4, lines 12-18; and page 5, lines 8-16.

The Examiner's conclusory statements do not provide sufficient evidence of motivation to combine to support a *prima facie* case of obviousness. In particular, the Examiner has not pointed out any specific reason why one of ordinary skill in the art, without the benefit of Appellants' disclosure, would select Baichwal's excipient from the thousands of known controlled release delivery systems for use in the two-part enantiomer formulations of Gilbert. Conclusory statements regarding the general advantages of Baichwal's excipient (*e.g.*, noting that it is inexpensive and can be used with a variety of drugs) do not suffice in view of the vast

number of available controlled release technologies, each of which may have their own particular advantages.

Appellants' response dated May 8, 2003 described a review of the PTO patent database at www.uspto.gov for patents issued from 1976 to May 6, 2003. Boolean searches of the database revealed **22,097** hits for the terms "controlled," "release," and "pharmaceutical"; **17,479** hits for the terms "sustained," "release," and "pharmaceutical"; and **11,214** hits for the terms "extended," and "release," and "pharmaceutical." In view of these search results, Appellants respectfully requested an explanation why one skilled in the art would be motivated to select Baichwal from among the more than 22,000 patents from 1976 to the present in the PTO database that describe conventional controlled-release technology. *See* Response and Amendment of May 8, 2003 at page 9, line 29 – page 10, line 8. In the Final Office Action of July 24, 2003, the Examiner failed to provide the requested explanation, instead simply dismissing Appellants' search results as "very broad and unpersuasive." To support this position, the Examiner stated that Appellants provided no evidence that all of the 22,097 references found by the search teach a controlled release system, and rather showed only that the three words appeared in the same reference. *See* Final Office Action at page 5, lines 17-22.

To address the Examiner's concern about the relevance of the identified references, Appellants performed an additional search of the PTO patent database on December 5, 2003, using the following search query: ("controlled release formulation" or "sustained release formulation" or "extended release formulation") and "pharmaceutical." Even this much more limited search, which mandates that the identified references disclose a controlled release formulation, revealed **2,061** hits. It should be remembered that these search results represent only U.S. patents issued since 1976, and the broader patent and scientific literature would certainly provide many more relevant search results. In view of these additional search results, Appellants again respectfully submit that a clear explanation should be provided why one of ordinary skill in the art would select the Baichwal reference from among the thousands of available references disclosing conventional controlled release technology. Without such an explanation, Appellants maintain that there simply would have been no motivation for one of ordinary skill in the art to select the sustained release excipient of Baichwal for use in the formulation described by Gilbert.

Gilbert itself expands on a large number of potential dosage forms, including oral, rectal, transdermal, ophthalmic, pulmonary, and injectable formulations of various types, *e.g.*, multi-particulates, multiple tablets, osmotic pumps, bi-layered tablets, transdermal patches, polymer implants, and aerosols. *See* page 5, line 31 – page 8, line 8. As discussed above, in describing these dosage forms, Gilbert refers to adjusting the rate of release of the enantiomers using "any conventional controlled-release mechanism, for instance, matrix (ie. erosion diffusion), coating, or osmotic." *See, e.g.,* page 6, lines 9-14. In the Examples, Gilbert teaches controlled-release tablets and bi-layer tablets prepared with a particular controlled release excipient, namely, hydroxypropyl methyl cellulose (HPMC). *See* Examples 2-3, page 9, line 15 – page 10, line 17. The Examiner has not provided any reason why one of ordinary skill in the art would choose to prepare the formulations of Gilbert using any particular undisclosed conventional controlled release technology, rather than simply using HPMC, which Gilbert specifically teaches and exemplifies.

In sum, given the extremely large number of "conventional controlled release mechanisms," and Gilbert's exemplification of HPMC in particular, there would be no motivation to select the particular excipient of Baichwal for use in Gilbert's two-part formulations. In the absence of any motivation to combine the cited references, Appellants' claims are not obvious over Gilbert in view of Baichwal. *See In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (claimed compound not obvious where cited reference teaches vast number of compounds and discloses typical or preferred compounds different from claimed compound, and thus does not suggest selection of claimed compound) (citing *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) (claimed nucleic acid sequences not obvious over reference teaching almost infinite possibilities and not suggesting why one would choose the claimed sequences)); *In re Herschler*, 591 F.2d 693, 702 (C.C.P.A. 1979) (claimed combination of steroid and solvent DMSO not obvious where references teach general utility of DMSO as a solvent but there is no suggestion to choose DMSO from among countless numbers of solvents).

The U.S. Court of Appeals for the Federal Circuit has warned that it is improper to "use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Furthermore, "the best defense against hindsight-based obviousness analysis is rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art

references." *Ecolochem, Inc. v. Southern California Edison Co.*, 277 F.3d 1361, 1371 (Fed. Cir. 2000) (citation omitted). With respect to Appellants' claimed invention, there has been no showing of any motivation to combine the cited references, so *prima facie* obviousness has not been established, and the obviousness rejection is improper.

Accordingly, Appellants request that the Board of Patent Appeals and Interferences reverse the rejection under 35 U.S.C. § 103, and remand this case to the Examiner to withdraw the rejection and enter a Notice of Allowance.

## IX. CONCLUSION

For the reasons advanced above, Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejection, remand the application to the Examiner, and direct the Examiner to issue a Notice of Allowance.

Please deduct the $165.00 fee for filing an appeal brief from our Deposit Account No. 08-0219. No other fees are believed to be due. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

Respectfully Submitted,

Emily R Whelan

Emily R. Whelan
Registration No. 50,391

Dated: 12/16/03

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## APPENDIX: Pending Claims

24. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of an immediate release formulation comprising a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof; and a controlled release formulation comprising a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a heteropolysaccharide and polysaccharide gum excipient.

25. The composition of claim 24, wherein the ratio of the heteropolysaccharide and polysaccharide gum excipient to (+) chiral compound enantiomer or pharmaceutically acceptable salt thereof is between about 1:3 to 3:1.

26. The composition of claim 24, wherein the heteropolysaccharide and polysaccharide gum excipient comprises locust bean gum and xanthan gum.

27. The composition of claim 24, wherein the controlled release formulation comprises a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose.

28. The composition of claim 24, wherein the controlled release formulation comprises a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 15% locust bean gum, 15% xanthan gum, 60% dextrose, and 10% calcium sulfate.

29. The composition of claim 24, wherein the composition is a bi-layered tablet.

30. The composition of claim 24, wherein the compound of the (+) and (-) chiral compound enantiomers is selected from the group consisting of warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine, aminoglutethimide, alfuzosin, celiprolol, cisapride, disopyramide, fenoldopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thioctic acid, thiopental, and zacopride.

31. The composition of claim 24, wherein, when measured by the USP type II dissolution method, the *in vitro* dissolution rate for the controlled release (CR) formulation and the immediate release (IR) formulation are:

| Time (hours) | % CR Release | % IR Release |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-60 % | 20-100 % |
| 0.5 | 0-65 % | 20-100 % |
| 1.0 | 5-70 % | 25-100 % |
| 2.0 | 5-75 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 10-100 % | 30-100 % |
| 8.0 | 20-100 % | 40-100 % |
| 10.0 | 25-100 % | 45-100 % |
| 12.0 | 25-100 % | 45-100 % |
| 18.0 | 35-100 % | 50-100 % |
| 24.0 | 35-100 % | 50-100 %. |

32. The composition of claim 24, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at different mass quantities.

33. The composition of claim 24, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at a percent ratio selected from the following table:

| (+) enantiomer | (-) enantiomer |
|---|---|
| 2 | 1 |
| 3 | 1 |
| 4 | 1 |
| 5 | 1 |
| 10 | 1 |
| 1 | 2 |
| 1 | 3 |
| 1 | 4 |
| 1 | 5 |
| 1 | 10. |

34. The composition of claim 24, wherein about 90% of the (+) chiral compound enantiomer and about 90% of the (-) chiral compound enantiomer are released within about 12 hours of administration.

35. The composition of claim 24, wherein when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral compound enantiomer plasma concentrations:

| Time (hours) | (+) Enantiomer | (-) Enantiomer |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-60 % | 0-100 % |
| 0.5 | 0-65 % | 0-100 % |
| 1.0 | 5-70 % | 25-100 % |
| 2.0 | 5-75 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 20-100 % | 30-100 % |
| 8.0 | 20-100 % | 20-100 % |
| 10.0 | 20-100 % | 20-100 % |
| 12.0 | 10-100 % | 0-90 % |
| 18.0 | 0-80 % | 0-80 % |
| 24.0 | 0-80 % | 0-80 %. |

36. The composition of claim 24, wherein, when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral drug enantiomer plasma concentrations:

| Time (hours) | (+) Enantiomer | (-) Enantiomer |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-40 % | 0-100 % |
| 0.5 | 0-45 % | 0-100 % |
| 1.0 | 5-50 % | 25-100 % |
| 2.0 | 5-55 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |

| | | |
|---|---|---|
| 6.0 | 20-100 % | 30-100 % |
| 8.0 | 20-100 % | 20-100 % |
| 10.0 | 10-100 % | 20-100 % |
| 12.0 | 0-80 % | 10-90 % |
| 18.0 | 0-80 % | 0-80 % |
| 24.0 | 0-80 % | 0-80 %. |

37. The composition of claim 24, wherein the compound of the (+) and (-) chiral compound enantiomers is tramadol.

38. The composition of claim 37, wherein the (+) tramadol enantiomer and the (-) tramadol enantiomer are present in the composition at a percent ratio of 3:1.

39. The composition of claim 37, wherein the (+) tramadol enantiomer and the (-) tramadol enantiomer are present in the composition at a percent ratio of 2:1.

40. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of an immediate release formulation comprising a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof; and a controlled release formulation comprising a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a heteropolysaccharide and polysaccharide gum excipient.

41. The composition of claim 40, wherein the ratio of the heteropolysaccharide and polysaccharide gum excipient to (-) chiral compound enantiomer or pharmaceutically acceptable salt thereof is between about 1:3 to 3:1.

42. The composition of claim 40, wherein the heteropolysaccharide and polysaccharide gum excipient comprises locust bean gum and xanthan gum.

43. The composition of claim 40, wherein the controlled release formulation comprises a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose.

44. The composition of claim 40, wherein the controlled release formulation comprises a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 15% locust bean gum, 15% xanthan gum, 60% dextrose, and 10% calcium sulfate.

45. The composition of claim 40, wherein the composition is a bi-layered tablet.

46. The composition of claim 40, wherein the compound of the (+) and (-) chiral compound enantiomers is selected from the group consisting of warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine, aminoglutethimide, alfuzosin, celiprolol, cisapride, disopyramide, fenoldopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thioctic acid, thiopental, and zacopride.

47. The composition of claim 40, wherein, when measured by the USP type II dissolution method, the *in vitro* dissolution rate for the controlled release (CR) formulation and the immediate release (IR) formulation are:

| Time (hours) | % CR Release | % IR Release |
|---|---|---|
| 0 | 0% | 0% |

| | | |
|---|---|---|
| 0.3 | 0-60 % | 20-100 % |
| 0.5 | 0-65 % | 20-100 % |
| 1.0 | 5-70 % | 25-100 % |
| 2.0 | 5-75 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 10-100 % | 30-100 % |
| 8.0 | 20-100 % | 40-100 % |
| 10.0 | 25-100 % | 45-100 % |
| 12.0 | 25-100 % | 45-100 % |
| 18.0 | 35-100 % | 50-100 % |
| 24.0 | 35-100 % | 50-100 %. |

48. The composition of claim 40, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at different mass quantities.

49. The composition of claim 40, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at a percent ratio selected from the following table:

| (+) enantiomer | (-) enantiomer |
|---|---|
| 2 | 1 |
| 3 | 1 |
| 4 | 1 |
| 5 | 1 |
| 10 | 1 |

| | |
|---|---|
| 1 | 2 |
| 1 | 3 |
| 1 | 4 |
| 1 | 5 |
| 1 | 10. |

50. The composition of claim 40, wherein about 90% of the (+) chiral compound enantiomer and about 90% of the (-) chiral compound enantiomer are released within about 12 hours of administration.

51. The composition of claim 40, wherein when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral compound enantiomer plasma concentrations:

| Time (hours) | (+) Enantiomer | (-) Enantiomer |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-60 % | 0-100 % |
| 0.5 | 0-65 % | 0-100 % |
| 1.0 | 5-70 % | 25-100 % |
| 2.0 | 5-75 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 20-100 % | 30-100 % |
| 8.0 | 20-100 % | 20-100 % |
| 10.0 | 20-100 % | 20-100 % |
| 12.0 | 10-100 % | 0-90 % |

| | | |
|---|---|---|
| 18.0 | 0-80 % | 0-80 % |
| 24.0 | 0-80 % | 0-80 %. |

52. The composition of claim 40, wherein, when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral drug enantiomer plasma concentrations:

| Time (hours) | (+) Enantiomer | (-) Enantiomer |
|---|---|---|
| 0 | 0% | 0% |
| 0.3 | 0-40 % | 0-100 % |
| 0.5 | 0-45 % | 0-100 % |
| 1.0 | 5-50 % | 25-100 % |
| 2.0 | 5-55 % | 25-100 % |
| 4.0 | 10-80 % | 30-100 % |
| 6.0 | 20-100 % | 30-100 % |
| 8.0 | 20-100 % | 20-100 % |
| 10.0 | 10-100 % | 20-100 % |
| 12.0 | 0-80 % | 10-90 % |
| 18.0 | 0-80 % | 0-80 % |
| 24.0 | 0-80 % | 0-80 %. |

53. The composition of claim 40, wherein the compound is tramadol.

54. A bi-layered, orally administrable tablet comprising:

(a) a controlled release formulation comprising about 5.4% by weight (+) tramadol or a pharmaceutically acceptable salt thereof; about 37.7% by weight of a controlled release

delivery system; about 16.2% by weight silicified microcrystalline cellulose; and about 0.6% by weight magnesium stearate; wherein the controlled release delivery system comprises 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose; and

(b) an immediate release formulation comprising about 16.2% by weight (-) tramadol or a pharmaceutically acceptable salt thereof; about 10.8% by weight silicified microcrystalline cellulose; about 10.8% lactose fast flow; about 2.2% sodium starch glycolate and about 0.3 % by weight magnesium stearate;

wherein the % by weight is based on the weight of the bi-layered, orally administrable tablet.